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(21) International Application Number: PCT/EP93/01508 (22) International Filing Date: 15 June 1993 (15.06.93) (30) Priority data: M192A001601 30 June 1992 (30.06.92) IT (71) Applicant (for all designated States except US): MONTERESEARCH S.R.L. [IT/IT]; Via G. Galilei, 7, I-20016 Pero (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): BERLATI, Fabio [IT/IT]; CESCHEL, Giancarlo [IT/IT]; RODA, Aldo [IT/IT]; RODA, Enrico [IT/IT]; RONCHI, Celestino [IT/IT]; Via G. Galilei, 7, I-20016 Pero (IT). (74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: THE USE OF NOR- AND HOMO- BILE ACIDS DERIVATIVES AS ABSORPTION ENHANCERS FOR MEDICAMENTS (57) Abstract The use of nor- and homo- bile acids derivatives as absorption enhancers for medicaments. Said derivatives show the advantage of improving the absorption of medicaments through mucosae without being metabolized by the intestinal flora, thus allowing a fast excretion. Moreover, the derivatives of the invention have a negligible toxicity.		

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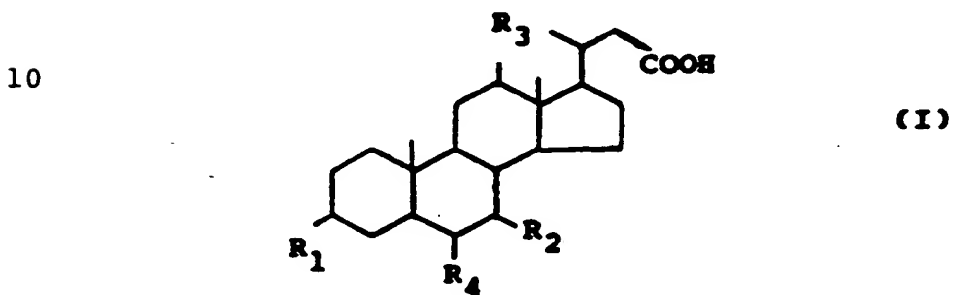
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THE USE OF NOR- AND HOMO- BILE ACIDS DERIVATIVES AS
ABSORPTION ENHANCERS FOR MEDICAMENTS

The present invention relates to the use of nor- and homo- bile acids derivatives (hereinafter named NORAB and HOMOAB, respectively) as absorption enhancers for medicaments.

Particularly, the invention relates to the use of nor- and homo- bile acids derivatives having respectively the following formulae:



15 wherein:

	R ₁	R ₂	R ₃	R ₄
a)	α-OH	α-OH	H	H
b)	α-OH	β-OH	H	H
c)	α-OH	H	α-OH	H
20 d)	α-OH	H	β-OH	H
e)	α-OH	H	H	β-OH

corresponding to:

Ia) norchenodeoxycholic acid

Ib) norursodeoxycholic acid

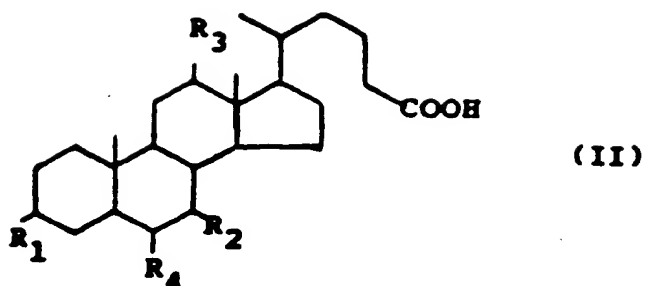
25 Ic) nordeoxycholic acid

Id) 24-nor-[3α,12β-dihydroxy-5β-cholan-23-oic] acid

Ie) 24-nor-[3α,6β-dihydroxy-5β-cholan-23-oic] acid

and

2



5

wherein:

	R_1	R_2	R_3	R_4
10 f)	α -OH	α -OH	H	H
g)	α -OH	β -OH	H	H
h)	α -OH	H	α -OH	H
i)	α -OH	H	β -OH	H
l)	α -OH	H	H	β -OH

15 corresponding to:

II f) homochenodeoxycholic acid

II g) homoursodeoxycholic acid

II h) homodeoxycholic acid

III i) 24-homo-[3 α ,12 β -dihydroxy-5 β -cholan-23-oic] acid20 III l) 24-homo[3 α ,6 β -dihydroxy-5 β -cholan-23-oic] acid.

It is also an object of the invention the use of the corresponding NORAB and HOMOAB conjugated respectively in C₂₃ and C₂₅ with taurine, glycine and alanine.

The present trend for pharmacological therapy, particularly in the case of slight disorders or of treatments involving multiple administrations repeated in time, and therapies for conscious patients, is the self-administration by the patient itself. From this point of view, the preferred administration routes are the enteral, i.e. buccal, rectal and intranasal ones.

30

The medicament administered through these routes,

once released from the pharmaceutical form containing it (tablet, suppository, aerosol, and the like), must cross the different mucosae coating the gastrointestinal tract and the nasal cavity, in order to enter the circulatory stream and be distributed in the various body districts thus reaching the action site.

Due to the complex nature of the mucosae and the different chemical structure of the medicaments, the crossing of the mucosae involves different difficulties, depending on the kind of medicament and the type of mucosa.

One of the main problems involved in the design of medicaments consists in the need to give the pharmacologically active compound those hydrophilic characteristics which are generally required to have the active principle dissolved in the biological liquids (serum, interstitial liquid) and sometimes also lipophilic characteristics to cross the mucosa, which generally consists of a more or less complex cell barrier.

This approach finds a number of difficulties from the viewpoint of the medicament design, both in the synthesis and in the pharmacokinetic expectation.

A different approach to this problem consists in combining the active principle with a compound enhancing the absorption of the medicament through the mucosa.

Due to the single chemico-physical peculiarities of the different medicaments, up to now it was necessary to look for absorption enhancers suitable for both the considered medicament and the involved mucosa.

Bile acids (BA) are natural detergents capable of

forming, with other poorly water-soluble medicaments, mixed micells with phospholipids and cholesterol at a relatively low concentration (1-4 mM).

Moreover, thanks to the structure thereof, they
5 are also relatively lipophilic ($\log p = 2 \div 4$) and therefore they can passively cross the biologic membranes. The bile acids crossing and partitioning in the lipidic domain exert their activity in this microenvironment modifying the cholesterol content and
10 therefore increasing the permeability to other substances.

A bile acid designed to be an enhancer, moreover, must be:

- 1) relatively lipophilic, with a partition
15 coefficient octanol/water $\log P \geq 1$;
- 2) relatively detergent, with a critical micell concentration $\leq 7 \pm 2$ mM;
- 3) stable to intestinal bacterial flora and particularly not 7-dehydroxylated and oxidized to
20 potentially toxic or inactive compounds.

Now it has been found that bile acids derivatives in which the side chain has one carbon atom more (NOR) or one less (HOMO) proved remarkable properties as absorption enhancers for medicaments by the enteral
25 route and other not-parenteral routes (intranasal, buccal, sublingual).

Particularly, the best results were obtained with derivatives of the dehydroxylated bile acids above reported with two OH at the 3 α 7 α , 3 α 7 β , 3 α 6 α , 3 α 12 α and
30 3 α 12 β positions. The choice of one of the above reported epimers will depend on the substance to carry.

Compared with the natural derivatives, the nor- and homo-derivatives show the advantage that they are not metabolized by the intestinal bacterial flora and have a very high stability in anaerobic and aerobic fecal culture.

The change in the side chain can prevent a 7 dehydroxylation of the 3 α 7 α and 3 α 7 β derivatives with an enormous advantage compared with the natural components which are quickly metabolized.

The glycine- or taurine- amidated compounds also show a high stability to bacterial flora compared with physiological bile acids (BA) which are quickly deconjugated.

The derivatives of the invention are useful as absorption enhancers for medicaments administered by the enteral route or by other routes (intranasal, buccal, sublingual).

One of the most preferred administration routes is the rectal one, since these compounds are absorbed by the rectal mucosa and, once in circulation, they are immediately transformed into glucuronide derivatives at the hepatic level and excreted through the feces (even though they are not metabolized by the bacteria in the last intestinal tract, as already mentioned).

The general toxicity thereof is negligible even at doses 100 times higher than the envisaged ones.

The compounds of the invention can be obtained semisynthetically according to known methods.

The medicaments which can be advantageously combined with iodeoxycholic acid belong in various chemical and/or therapeutical classes, such as

peptides, not steroidal antiinflammatories, steroids, diuretics, cardiovasculars, hormones, local anaesthetics, antihistaminics, rhinologic and anticolinergic agents.

5 NORAB and HOMOAB, compared with the up to now known enhancers, particularly with other bile acids previously used (cholic and taurocholic acids) show the following advantages:

- higher effectiveness;
- 10 - lower toxicity;
- metabolic stability towards the bacterial flora responsible for undesired biotransformations, such as the conversion of taurocholic acid into deoxycholic acid;
- 15 - optimum lipohilia for the increase in cell membrane permeability, thanks to the capability of forming reverse micells inside which a part of membrane cholesterol dissolves, thereby the membrane becoming more permeable;
- 20 - low detergency, which therefore causes no damages nor inflammations.

Examples of rectal formulations according to the invention comprise suppositories, microclysmas, soft gelatin rectal capsules.

25 For the intranasal administration, sterile solutions or powders are suitable, whereas oral or buccal forms comprise capsules, tablets, bioadhesive tablets and the like.

The preparation techniques and the excipients used
30 for the preparation of said pharmaceutical forms are the conventional ones known, for example, from

Remington's Pharmaceutical Sciences, Mack Pub., Co.,
N.Y., USA, XVII Ed.

For the oral use, the presence of NORAB and/or
HOMOAB enhances the absorption of some active
5 principles such as NSADs, diuretics and the like.

For the oral administration, the action of the
derivatives of the invention takes place mainly at the
duodenal and intestinal levels, therefore, in order to
optimize the absorption, gastroresistant forms or
10 controlled-release forms are preferably used, allowing
the tablet to disintegrate at well-controlled pH values
which are characteristic of a particular portion of the
intestinal tract.

According to the invention, NORABs and HOMOABs are
15 used in amounts from 0.1 to 100 mg per unitary dose.
Preferably, for the oral, buccal and rectal forms, they
are present in amounts from 10 to 40 mg per unitary
dose, whereas for intranasal forms they range from 0.5
to 10 mg per unitary dose.

20 The following examples further illustrate the
invention. In said examples, Enhancer HOMOAB1, Enhancer
NORAB1, Enhancer HOMOAB2, Enhancer NORAB2, Enhancer
HOMOAB3, Enhancer NORAB4, Enhancer HOMOAB5 and Enhancer
NORAB5 means, respectively, the following acids:
25 homochenodeoxycholic, norchenodeoxycholic, homoursodeo-
xycholic, norursodeoxycholic, homodeoxycholic, 24-nor-
[3 α ,12 β -dihydroxy-5 β -cholan-23-oic], 24-homo-[3 α -6 β -
dihydroxy-5 β -cholan-23-oic] and 24-nor[3 α -6 β -dihydroxy-
5 β -cholan-23-oic].

30

EXAMPLE 1**Diclofenac suppositories**

One suppository contains:

Sodium diclofenac	100	mg
Enhancer HOMOAB1	20	mg
Whitepsol H 15	q.s. to	2,5 g

5

EXAMPLE 2Calcitonin rectal capsules

One soft gelatin capsule for rectal use contains:

Synthetic salmon calcitonin	100	I.U.
Enhancer NORAB1	20	mg
Vaseline oil	q.s. to	700 mg

10

EXAMPLE 3Dipyrone coated tablets

One coated tablet contains:

15	Dipyrone	250	mg
	Starch	125	mg
	Enhancer HOMOAB2	100	mg
	Microcrystalline cellulose	150	mg
	Talc	30	mg
20	Magnesium stearate	20	mg
	PVP K30	30	mg
	Methacrylic acid polymer	10	mg
	Diethyl phthalate	0,5	mg

EXAMPLE 4Furosemide tablets

One tablet contains:

	Furosemide	20	mg
	Enhancer NORAB2	20	mg
	Starch	50	mg
30	Lactose	50	mg
	PVP K30	3	mg

Talc	1 mg
Magnesium stearate	1 mg
Croscarmellose	5 mg

EXAMPLE 5

5	<u>Metronidazole tablets</u>	
	One tablet contains:	
	Metronidazole	250 mg
	Microcrystalline cellulose	200 mg
	Starch	130 mg
10	Enhancer HOMOAB3	100 mg
	Talc	10 mg
	Sodium amidoglycolate	100 mg

EXAMPLE 6

	<u>LHRH for buccal use:</u>	
15	One administration unit contains:	
	LHRH	50 mcg
	Starch	80 mg
	Carboxyvinyl polymer	100 mg
	Enhancer NORAB4	20 mg

EXAMPLE 7

20	<u>LHRH for intranasal administration:</u>	
	One administration unit contains:	
	LHRH	50 mcg
	Enhancer HOMOAB5	5 mg
25	Mannite	q.s. to 20 mg

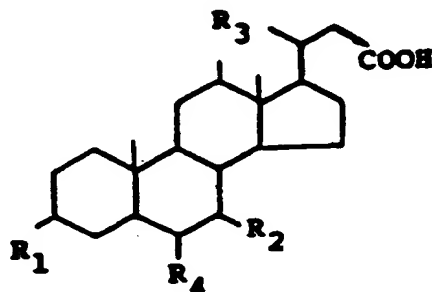
EXAMPLE 8

	<u>GRH for intranasal administration:</u>	
	One administration unit contains:	
	GRH	50 mcg
30	Enhancer NORAB5	2,5 mg
	Mannite	q.s. to 20 mg

CLAIMS

1. The use of nor- and homo- bile acids derivatives
and of the conjugated thereof in C₂₃ and C₂₅ with
5 taurine, glycine and alanine as absorption enhancers
for medicaments.

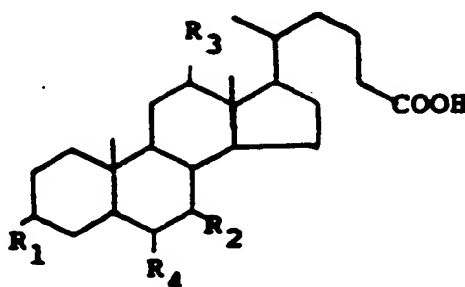
2. The use of nor- and homo- bile acids derivatives
and of the conjugated thereof in C₂₃ and C₂₅ with
10 taurine, glycine and alanine, having the following
formulae:



(I)

wherein:

	R ₁	R ₂	R ₃	R ₄
20 a)	α-OH	α-OH	H	H
b)	α-OH	β-OH	H	H
c)	α-OH	H	α-OH	H
d)	α-OH	H	β-OH	H
e)	α-OH	H	H	β-OH



(II)

wherein:

	R ₁	R ₂	R ₃	R ₄
f)	α -OH	α -OH	H	H
g)	α -OH	β -OH	H	H
5 h)	α -OH	H	α -OH	H
i)	α -OH	H	β -OH	H
l)	α -OH	H	H	β -OH

as absorption enhancers for medicaments.

3. The use according to claims 1-2, characterized in
10 that the absorption takes place in the gastrointestinal tract.

4. The use according to claim 3, characterized in that the absorption takes place at the buccal mucosa level.

15 5. The use according to claim 3, characterized in that the absorption takes place in the duodenal tract.

6. The use according to claim 3, characterized in that the absorption takes place in the intestinal tract.

20 7. The use according to claim 3, characterized in that the absorption takes place in the rectal tract.

8. The use according to claims 1-2, characterized in that the absorption takes place in the intranasal cavity.

25 9. The use according to claims 1-8, characterized in that the medicaments are selected from peptides, not steroidal antiinflammatories, steroids, diuretics, cardiovasculars, hormones, local anaesthetics, antihistaminics, rhinologics, anticholinergics.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/01508

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K47/28

II. FIELDS SEARCHEDMinimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸**III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹**

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 135 782 (LEHNER A.G.) 3 April 1985 see claims see page 1, line 20 - line 24 see page 2, line 19 - line 21 see page 12, line 4 - line 14 ----	1-9
A	EP,A,0 128 831 (M.C.CAREY) 19 December 1984 see claims -----	1-9

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IV. CERTIFICATION

Date of the Actual Completion of the International Search 22 SEPTEMBER 1993	Date of Mailing of this International Search Report 30.09.93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer SCARPONI U.

Form PCT/ISA/210 (second sheet) (January 1985)

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9301508
SA 76009

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		JP-C- 1561393	31-05-90
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